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# Preparation of the Anti-Inflammatory Bigel and Comparative Study of Drug Release Between Human Cadaver Skin and Rats Abdominal Skin

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This study investigates the development of ketoprofen bigel for transdermal route to reduce the inflammation.The benefits of transdermal administration increase the compliance in elderly patients with chronic conditions such as Osteoarthritis and Rheumatoid arthritis.Linseed oilis being added owning to itsanalgesic and anti-inflammatory property, while menthol is incorporated due its local vasodilator agent, which could possiblyprovide formulation with cooling sensation, thereby could result in rapid pain reduction.The prepared formulations were evaluated for in-vitro diffusion studies using artificial membrane, while the most important ex-vivo studies were carried out using human cadaver skin.The desired drug permeation was obtained by optimizing the ketoprofen bigel formulations. The crucial pharmaceutical requirement studies were carried out on the prepared Bigel formulations. All the formulations showed good clarity and homogeneity. The spreadability results obtained were in correlation to the amount of polymers being added. Comparative studies of drug release is carried out between human cadaver skin and rat's abdominal skin. The drug release from bigel formulationswerein the range of 96.65 - 99.83%respectively through cellophane membrane, while that of human cadaver skin was found to be 71.3% at the end of 4 hours of studies and .In conclusion, the combination of ketoprofen with linseed oil and menthol can rapid permeate skin well, which could be significantly beneficial in the management of pain & inflammation.

**Keywords:** Ketoprofen, Vasodilator, bigel, human cadaver skin, ex-vivo studies.

## 1. Introduction

Ketoprofen is a derivative of propionic acid which belongs to non - steroidal anti-inflammatory drugs (NSAID). Ketoprofen possess analgesic, anti –pyretic and anti-inflammatory properties. It is used in the management of inflammation in joints and muscles, osteoarthritis, joint stiffness. There seems to be systemic side effects associated with ketoprofen which is to be taken orally,gastroinstestinal disturbances are more frequent as compare to other NSAIDS.Topical and transdermal formulation can overcome the side effects of ketoprofen

which are caused by oral ketoprofen formulations. Usually acute to chronic pain caused by osteoarthritis and rheumatoid arthritis. Accute inflammation is defined as immediate response of the body to injury or cell death(Willey et al., 2008). Histamine and prostaglandins are the chemical mediators which regulates inflammation. Ketoprofen acts on cyclooxygenase-2 which is an enzyme involved in the prostaglandin synthesis and cause inhibitory activity. Topical and transdermal treatments using NSAIDS having many advantages such as protection of the active pharmaceutical ingredient from gastric enzymes, escaping of the hepatic first-pass effect, and minimizes risk of gastrointestinal side effects such as ulcer, bleeding, and perforation. Bi-gels are somewhat new as compared to other gel formulations. These are uniform semisolid dispersion system, that contains two gel phases, are mixed together with the help of high shear rate and appear as a single gel phase visually. Bigel is the novel formulation which can be used in controlled drug delivery system.For assessing the efficiency of the optimized formulation animal models are used. The degree of edema, pain and analgesia in the rats paw or joint is determined by the investigator. Hot plate method and tail flick methods arecommonly used to evaluate to evaluate analgesic effect of the formulation. Fordetermining anti-inflammatory activity, carrageenan induced paw edema method is used.

## 2. Material and methods:

Ketoprofen, Carbopol 934, HPMC K100, Tri-ethanolmine and ethanol was purchased from swaroop pharmaceuticals. (Chhatrapati Sambhajinagar, India). All chemicals used during research were of analytical grade.

Pre- formulation studies:

Characterization of Ketoprofen:

Appearance:

The sample of Ketoprofen was tested for its colour, odour and taste.

Melting point:

Thiel's tube apparatus was used to determine melting point of the ketoprofen.

Solubility:

An excess amount of ketoprofen was added to 100 ml of different chemicals like methanol, ethanol, phosphate buffer and acetate buffer. These solutions were kept on a rotary shaker for about 48 hours at100 rpm. After 48 hours these solutions were filtered using whatman's filter paper. The filtrates were diluted with respective chemicals ie methanol, ethanol, phosphate buffer, acetate buffer and quantified by using U.v spectrophotometer at 256nm.

Uv spectrophotometric evaluation:

For determining absorption maxima ketoprofen was dissolved in methanol to make stock solution and from this stock solution different concentrations were prepared by further diluting these solutions with methanol . From these solutions one solution was taken and scanned from 200- 400nm. Absorption maxima was found at 256nm. The absorption maxima and calibration curve was given in a figure no.(1,2).

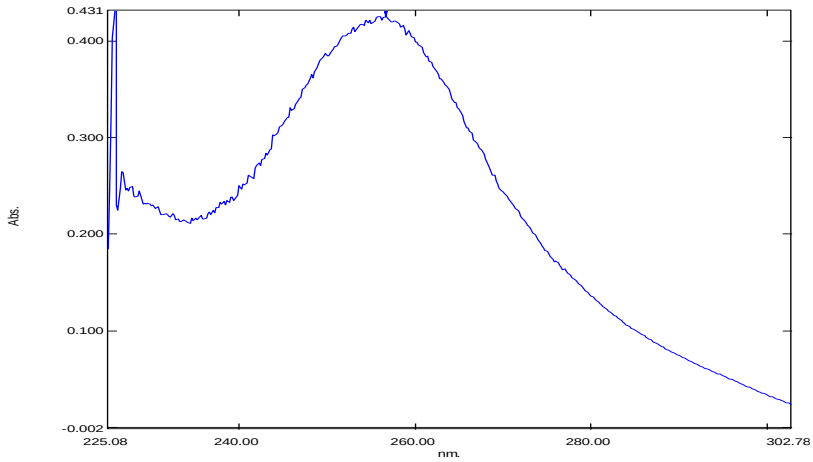



Figure no. 1. Absorption maxima of ketoprofen

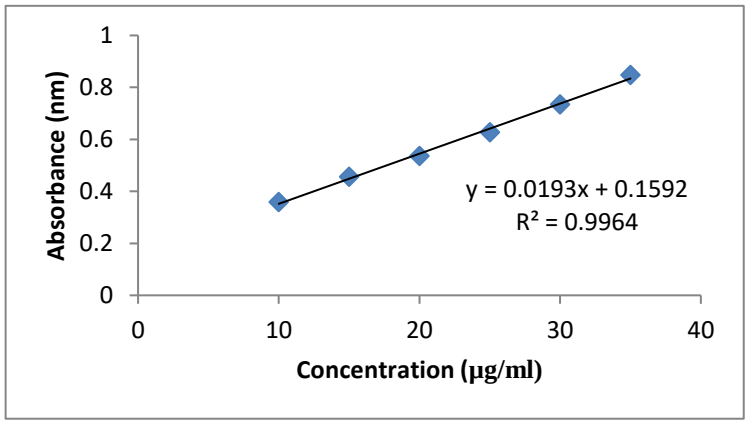



Figure no.2. Calibration curve and linear regression equation of ketoprofen at 256nm

FT-IR Spectrophotometric determination:

For checking the purity of drug FT-IR of the drug sample was done. Drug and excipients compatibility is also evaluated using FT-IR spectrometer using Shimadzu 8400-S, Japan. Two percent (w/w) of the sample with respect to a potassium bromide disc was mixed with dry KBr. The mixture was grind into a fine powder using an agate mortar and then compressed into a KBr disc in a hydraulic press at a pressure of 1000psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm-1 using cosine apodization. The characteristic peaks were recorded. FT-IR spectrum of drug polymer mixture & FT-IR of optimized bigel is given in a figure no. (3,4).

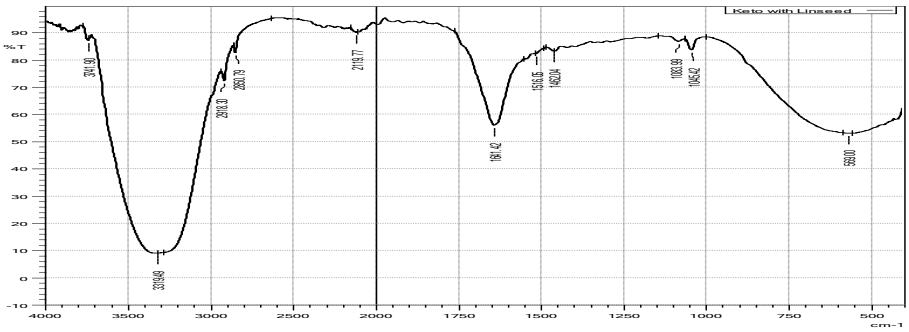



Figure no.3. FT-IR spectrum of optimized bigel formulation

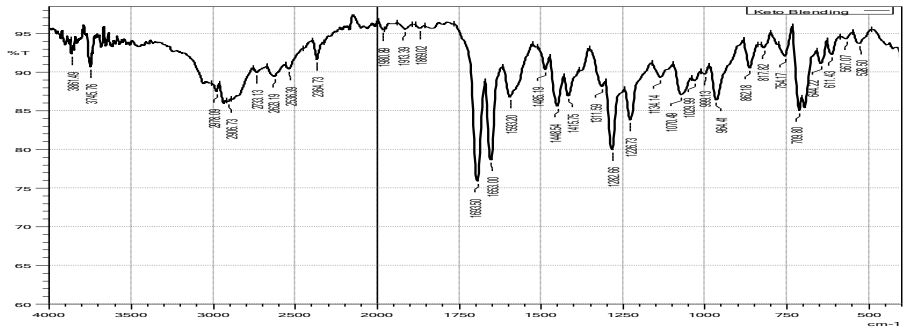



Figure no.4. FT-IR spectrum of ketoprofen with blend of excipients

DSC thermal analysis of the drug:

Thermal analysis was done for checking the purity of the drug sample. The study depicts a sharp endothermic peak at 92.99 °C that corresponds to melting point of the drug which shows the purity of the drug sample. Thermogram of the drug polymer mixture is given in a figure no.(5)

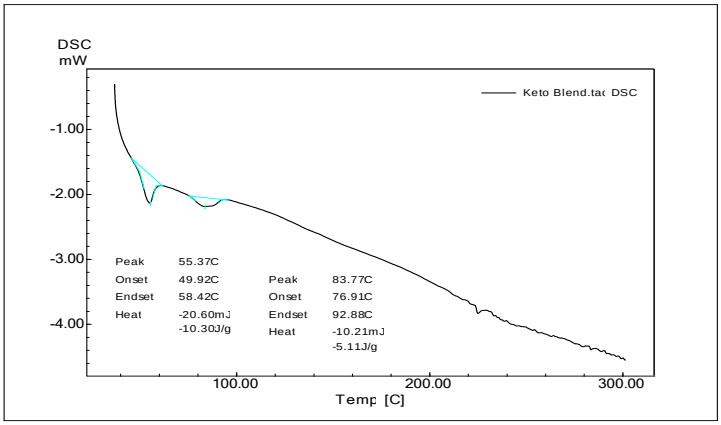



Figure no. 5. DSC thermogram of ketoprofen with blend of excipients

Preparation of ketoprofen bigel:

Bigel of ketoprofen is formed by using polymers like carbopol 934, HPMC K100, span 60 and linseed oil is used as a organogelator. Bigel is prepared by using two gels ie oleogel and hydrogel. It is a three step process in which first oleogel is prepared by using carbopol 934 which is dissolved in sufficient quantity of water and kept on magnetic stirrer for about 2 hours at 500 rpm. On the other-hand Span 60 was dissolved in a beaker on water bath, linseed oil was added to the beaker then the above carbopol 934 solution was taken tri-ethanolamine is added to this beaker and mixed to form a smooth olegel.

For hydrogel preparation HPMC K100 was taken in a beaker containing sufficient amount of water and kept for about 2 hours on magnetic stirrer at 500 rpm. The drug was dissolved in sufficient quantity of ethanol, menthol was also added to this. After 2 hours HPMC K100 was also added to this mixture to form a hydrogel.

Bigel was formulated by the addition of hydrogel in the formed oleogel under mechanical stirring at 1000 rpm. Different batches were formulated (KL1, KL2, KL3, KL4, KL5, KL6, KL7, KL8) and evaluated. As given in a table no. (1). Figure no. (10) shows optimized bigel.


Figure no.6. Optimized bigel formulation

Table no.1. Polymer concentration used in bigel

| Formulation code | Carbopol 934 (gm) | HPMC K100 (gm) | Span 60 (gm) |
|---|---|---|---|
| KL1 | 0.07 | 0.07 | 1.5 |
| KL2 | 0.06 | 0.08 | 2 |
| KL3 | 0.07 | 0.06 | 1 |
| KL4 | 0.08 | 0.08 | 2 |
| KL5 | 0.08 | 0.08 | 1 |
| KL6 | 0.08 | 0.06 | 2 |
| KL7 | 0.07 | 0.08 | 1 |
| KL8 | 0.08 | 0.06 | 1 |

Evaluation studies of bigels:

Appearance:Prepared bigels was evaluated for their appearance visually.

Homogeneity:All the batches of bigel was checked for presence of any lumps after they are being set into the containers. The results are given in a table no. (2).

PH measurement:DigitalpH meter was used to check the pH of bigels. The pH of all the batches were in the range of 7 – 7.5, that means it could not irritate the skin because the pH range comes under the limits of skin's pH. The results are shown in a table no. (2).

Spreadability:For checking the spreadability of the formulated bigel two glass slides were used to which pulley is attached to upper glassslide. These two glasses were placed on a wooden block. Required quantity of bigel is taken over a lower glass slide, to the pulley 50gram weight was added in a pan by this force upper glass slide moves over lower glass slide and the bigel is spread by slip and drag method.The time was noted when two glass slides separated. Formula for calculating spreadability is given blow:

$S = M. L / T$

Where M = wt. tied to upper slide L = length of glass slides T = time taken to separate the slides.

Spreadability results were given in a table no. (2).

Extrudability: Pfizer hardness tester was used for the determination of extrudability of the formulation. The formulated bigel (20gm) was filled in a alluminium collapsible tubeto which the plunger is attached and force (1 kg/cm²) is applied on alluminium tube to expel the bigel from tube. The quantity of bigel removed was weighed and the process was repeated three times at three different places on same tube. The results are shown in a table no. (2).

Viscosity determination:Brookfield(Brookfield Engineering Laboratories, Inc. USA). The formulation was evaluated for viscosity at a temperature (25- 27°C).The results of viscosity is given in a table no. (3).

In-vitro drug release evaluation:Phosphate buffer (pH 6.8) was used as a medium in a franz diffusion cell for checking in-vitro drug release of the drug. Cellulose membrane was used on which 1 gm of bigel was placed and this membrane was attached in between donor and receptor compartments. The assembly was placed on a magnetic stirrer at 600 rpm. The temperature of the medium was thermostatically controlled at 37 ± 0.5ºC which resembles to body temperature. 1 ml of the sample was removed from the sampling port at predetermined intervals and same volume was replaced by phosphate buffer. These removed samples were scanned under U.v spectroscopy at 256 nm and %In vitro drug release was calculated. The results are shown in a table no. (3) and figure no.(9).

Drug content determination:100 mg of formulated bigel was dissolved in a methanol and sonicate for 15 min. The solution was placed on a mechanical shaker for a period of about 2 hours. The solution was filtered through syringe filter (0.45µm). Required volume was taken and diluted with methanol and determined using U.v spectrophotometer at 256nm and % drug content was calculated. The results are given in a table no. (2).

Ex- vivo permeation of drug through human cadaver skin:

% Drug release from the bigel formulation was studied using human cadaver skin. Human cadaver skin was obtained from Government medical college and hospital Aurangabad. Franz diffusion cell was used to evaluate drug release, 2 cm human cadaver skin was taken 1 gm of bigel was placed on human cadaver skin. The skin is placed between donor and receptor compartment. The receptor compartment filled with phosphate buffer (pH 6.8) and temperature of the medium was thermostatically controlled by water jacket at 37 ± 0.5ºC. This assembly was placed on a magnetic stirrer at 500 rpm. At predetermined intervals samples were removed and same quantity was replaced by phosphate buffer. The absorbance of the sample was measured using U.v spectroscopy. % drug release was calculated. The results are given in a table no. (4) & figure no. (8). In figure no. (11) assembly of apparatus is given.

Ex-vivo permeation of drug through rat's abdominal skin:

Ex vivo studies were conducted using abdominal skin of albino rats (body weight of 250g and 12-13 weeks old female) purchased from Wokhardt Ltd. D-4, Chikalthana MIDC, Chhatrapati Sambhajinagar (approved ethical No:CPCSEA/IAEC/P'Ceutics/56/2023-24/181.The study was conducted in accordance with the guidelines for the care and use of laboratory animals. Rat was sacrificed to get the abdominal skin and hairs were removed by hair removal cream. The skin was made free from fatty debris and unwanted adhered tissues. The skin was placed between both chambers (donor and receptor) in such a way that the dermal side faced PBS medium (pH 7.4) and the epidermis faced upward on which bigel is applied (equivalent to 1 gram). The release medium was stirred using beads (500 rpm) at 37 ± 1 °C. Furthermore, sampling was performed at varied time points (0.5, 1, 2,3,4,5,6 hrs) and the drug release was determined. (31)

Stability studies:

According to ICH guidelines stability study of the formulated bigel was done. The bigel was filled into aluminium collapsible tubes and store at controlled temperature and humidity condition. The stability study was done for a period of three months. The temperatures and humidity conditions are 25 ± 2 ºC / 60 ± 5% RH, 30 ± 2 ºC / 65 ± 5% RH, 40 ± 2 ºC / 75 ± 5% RH.

The results shows that optimized bigel does not show any change in colour, pH, viscosity, extrudability, spreadability, % drug release. The results are given in a table no. (5).

## 3. Results and Discussion:

Ketoprofen bigel was prepared by changing concentrations of polymers. Different batches were prepared and evaluated.

Appearance:

All formulated bigels were white in colour and smooth in texture.

Homogeneity:

Formulated bigels were homogeneous, there is no grittiness present into the formulation. The results are given in table no. (2).

Table no. 2. Homogeneity, Spreadability, Extrudability Parameters, PH, Drug content

| Formulation code | Homogeneity | Spreadability | Extrudability | PH | Drug content (%) |
|---|---|---|---|---|---|
| KL1 | Excellent | 27.52 | + ++ | 7.51 | 99.41±0.16 |
| KL2 | Good | 25.41 | + + | 7.23 | 96.34±0.14 |
| KL3 | Excellent | 26.67 | + ++ | 7.48 | 99.23±0.22 |
| KL4 | Satisfactory | 20.13 | + | 6.72 | 95.42±0.13 |
| KL5 | Good | 23.71 | ++ | 7.37 | 97.66±0.25 |
| KL6 | Satisfactory | 19.26 | + | 6.83 | 95.32±0.23 |
| KL7 | Good | 24.33 | + + | 7.34 | 98.44±0.17 |
| KL8 | Good | 23.12 | + + | 7.46 | 97.24±0.20 |

pH:

PH of any formulation is important because a small change in pH can produce irritation or itchiness. The pH of all the prepared formulations are shown in table no. (2).

Spreadability:

The results obtained from spreadability tests it is proved that the bigel is easily spreadable when small force is applied. The prepared bigels KL1 TO KL8 are having the values in the range of 19.26-27.52g.cm/sec. KL1 is optimized formulation which shows good spreadability value. The results are given in a table no. (2).

Extrudability:

Extrudability is important characteristic of any semisolid preparation to remove the preparation from its container. KL1 formulation is having best extrudability and the results of extrudability is given in a table no. (2). KL1 formulation is having best extrudability.

Viscosity:

The viscosity of each batch was evaluated by Brookfield viscometer. The viscosity of batches were found in the range of 262000-402000 cps. The viscosity of the optimized KL1 bigel was 311000. The results of viscosity are shown in a table no. (3).

Table no. 3. Viscosity & In-vitro drug release

| Formulation code | Viscosity (cps) | In-vitro drug release (%) |
|---|---|---|
| KL1 | 311000 | 99.83 |
| KL2 | 308000 | 99.22 |
| KL3 | 262000 | 98.45 |
| KL4 | 402000 | 97.69 |
| KL5 | 380000 | 96.65 |
| KL6 | 313000 | 99.64 |
| KL7 | 262000 | 97.31 |

| | | |
|---|---|---|
| KL8 | 289000 | 98.45 |

In-vitro drug release:

% drug release of all the bigels was evaluated by using franz diffusion cell. The values of % drug release of batches KL1 TO KL8 is in the range of 96.65-99.83%. The KL1 formulation is optimized bigel which is having drug release 99.83%. The % release of the drug from formulation is given in a table no. (3)& drug release plot is shown in figure no. (9).

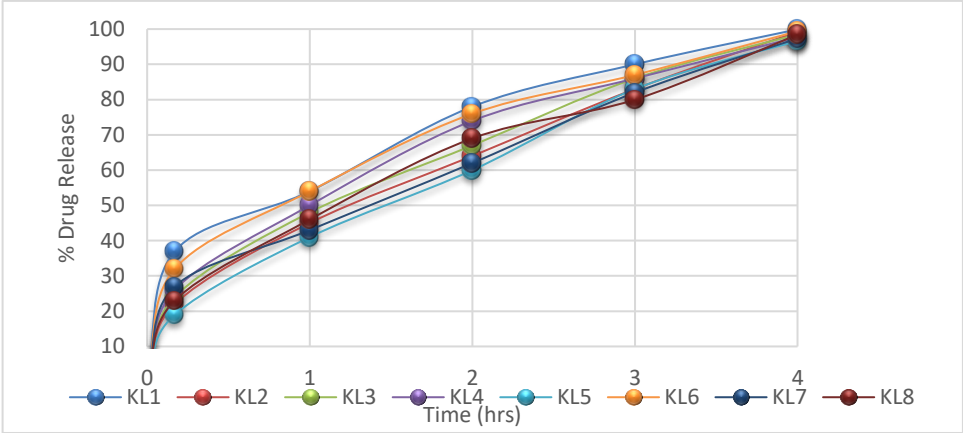



Figure 7. In-vitroPercent drug release of KL1 to KL8 bigel formulations

Drug content:

The percentage drug content which is present in the formulated bigel was evaluated by using U.V spectroscopy. The % drug content in the formulations were in the range of 94.25-99.16%. The results of drug content is shown in a table no. (2).

Ex- vivo permeation of drug through human cadaver skin and rat's abdominal skin:

The % drug release of the optimized KL1 formulation was determined using human cadaver skin. The optimized KL1 formulation shows drug release 71.314%. The plot of drug release is given in a figure no. (8) & % drug release is shown in a table no. (4).On the other-hand drug release through rat's abdominal skin was found to be 98.6%. The plot and figure of drug permeation is shown in table no.(5) & figure.no. (10). The differences in the drug release between human cadaver skin and rat's skin was found this may be due to the storage condition of human cadaver skin or may be due to the viability of the skin. Functional changes in the human cadaver skin may be occurred which hampered the drug release. While the drug release through rat's abdominal skin was good because fresh abdominal skin was taken and the animal is sacrificed for the study. In case of human cadaver skin the study is carried out for about 4 hours because after four hours no changes was absorbed in drug release where as drug release through rat's abdominal skin was done for about 6 hours because the formulation was releasing the drug till 6 hours of the application.

Table no. 4. Ex-vivo permeation of optimized KL1 bigel through human cadaver skin

| Sr.no | Time (hrs) | drug release (%) |
|---|---|---|
| 1 | 0 | 0.000 |
| 2 | 0.5 | 27.169 |
| 3 | 1 | 37.070 |
| 4 | 2 | 49.481 |
| 5 | 3 | 54.906 |
| 6 | 4 | 71.314 |

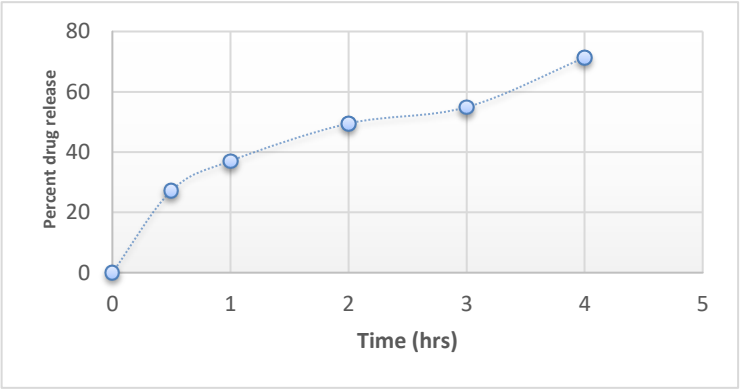
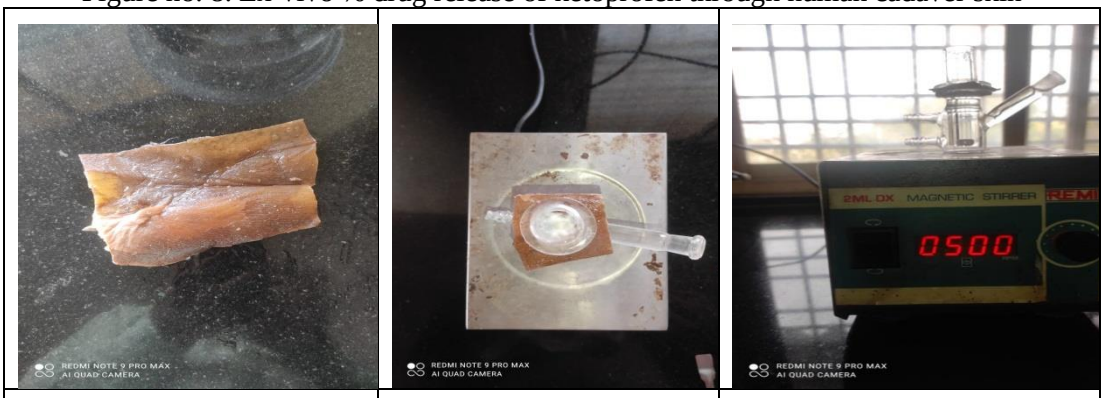



Figure no. 8. Ex-vivo % drug release of ketoprofen through human cadaver skin




| Human Cadaver Skin | Mounted cadaver skin over the diffusion cell | Diffusion studies |
|---|---|---|

Figure 9. Bigel Formulation KL1 showing in-vitro drug release through human cadaver skin

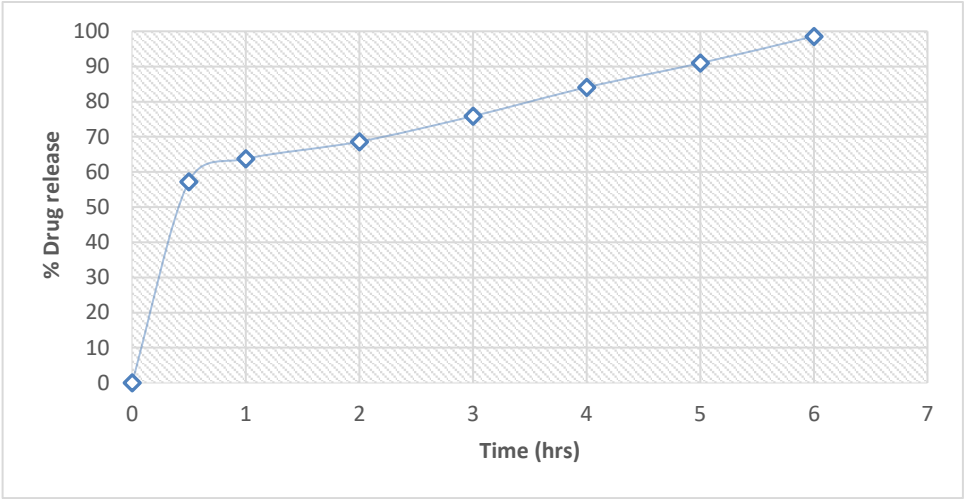



Figure 10. Drug release of KL1 through rat's abdominal skin

Table no.5. Drug permeation from optimized KL1 bigel through rats abdominal skin at different time intervals

| Time (hrs) | Drug release (%) |
|---|---|
| 0 | 0 |
| 0.5 | 57.2 |
| 1 | 63.7 |
| 2 | 68.6 |
| 3 | 75.9 |
| 4 | 84.1 |
| 5 | 90.9 |
| 6 | 98.6 |

Stability studies:

The optimize bigel formulation KL1 was studied for stability studies as per ICH guidelines. The optimized bigel formulation KL1 was kept at 25˚±2˚C/60±5%RH for first 30 days, after 30 days the bigel was kept at 40˚±2˚C/75±5%RH till 90 days.

The results shows that KL1bigel does not showsany change in colour, texture, viscosity, spreadability, extrudability, % drug release. The results are given in table no. (5).

Table no. 5. Stability determination of optimized bigel (KL1)

| Formulation code | No of Days | Temperature and Relative humidity | Colour and texture | pH | Drug Content (%) | Percent Drug release | Viscosity (cps) |
|---|---|---|---|---|---|---|---|
| KL1 | 0 | 25˚±2˚C/60±5%RH | White colour smooth texture | 7.50 | 99.49±0.16 | 99.83 | 311000 |
| KL1 | 15 | 25˚±2˚C/60±5%RH | White colour smooth texture | 7.50 | 99.49±0.16 | 99.83 | 311000 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| KL1 | 30 | 25˚±2˚C/60±5%RH | White colour smooth texture | 7.50 | 99.46±0.13 | 99.80 | 311000 |
| KL1 | 60 | 40˚±2˚C/75±5%RH | White colour smooth texture | 7.48 | 99.46±0.13 | 99.79 | 311000 |
| KL1 | 90 | 40˚±2˚C/75±5%RH | White colour smooth texture | 7.48 | 99.45±0.12 | 99.79 | 311000 |

## 4. Conclusion:

Ketoprofen drug is characterized by Uv spectroscopy to check its purity. Different concentrations were made by diluting the stock solution with suitable solvent, λmax was found at 256nm. In FT-IR analysis ketoprofen shows C-H stretching at 2937.59 $cm^{-1}$, O-H stretching was observed at 2731.20, c=o stretching was found at 1693.50, at 709.80 aromatic OH was found. DSC thermogram shows an endothermic peak at 97.25 °c which indicates melting point of the ketoprofen. Bigel was prepared by using polymers like carbopol 934 and HPMC K100 these polymers, linseed oil and other excipients used in formulation does not causes a change in ketoprofen which was observed by FT-IR. Linseed oil increase anti-inflammatory and analgesic activity of the formulation. All the prepared bigels are characterized by different tests. From these tests the best batch was chosen and further subjected for checking % drug release of the formulation. Human cadaver skin was used as a membrane in franz diffusion cell, 97.31% drug was released in 4 hours from the optimized bigel.

Conflict of interest:No

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